# Alkylation of cyclododecanone with α,ω-dibromoalkanes under conditions of phase-transfer catalysis

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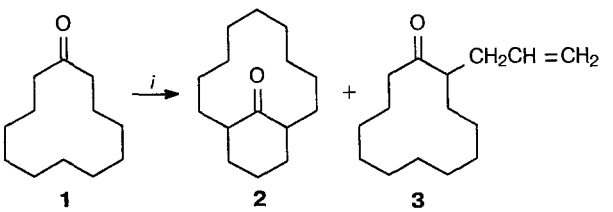
Alkylation of cyclododecanone with α,ω-dibromoalkanes $Br(CH)_nBr$ ($n$ = 3, 4, 5) under conditions of phase-transfer catalysis in the presence of KOH results in the formation of either bicyclic ketones for $n$ = 3 and 5 or a mixture of bicyclic and spirocyclic ketones for $n$ = 4.

**Key words:** alkylation; α,ω-dibromoalkanes; phase-transfer catalysis; cyclododecanone; bicyclo[9.3.0]pentadecan-15-one; bicyclo[9.4.1]hexadecan-16-one; bicyclo[9.5.1]heptadecan-17-one; 2-allyl-, 2-(3-bromopropyl)-, 2-(5-bromopentyl)-, 2-methylenecyclododecanone; 7-oxospiro[4.11]hexadecane; 7-oxospiro[5.11]heptadec-2-ene; 7-oxospiro[5.11]heptadecane.

Bicyclic ketones obtained from cyclododecanone, *e.g.*, bicyclo[9.3.1]pentadecan-15-one and bicyclo[9.4.1]-hexadecan-16-one, are starting materials in the syntheses of metacyclophanes[1,2] and macrocyclic ketones, *viz.*, cyclopentadecanone and muscone.[3]

The known syntheses of these bicyclic ketones based on 2-ethoxycarbonylcyclododecanone and sodium hydride involve several steps.[1,3]

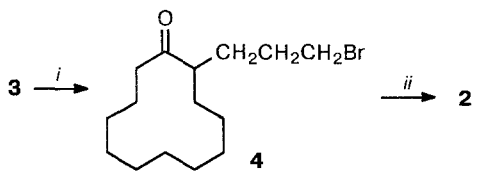
Previously, we have demonstrated that cyclododecanone can be easily alkylated with *n*-alkyl halides under conditions of phase-transfer catalysis giving rise to 2-alkylcyclododecanones.[4] In extension of these studies, alkylation of cyclododecanone (**1**) with α,ω-dibromoalkanes under analogous conditions was investigated. We aimed to obtain bicyclic ketones using this approach. We found that the reaction of 1,3-dibromopropane with ketone **1** in toluene at 80—100 °C in the presence of KOH and dibenzo-18-crown-6 (DCE) affords *trans*-bicyclo[9.3.1]pentadecan-15-one (**2**) and 2-allylcyclododecanone (**3**) in the ratio of 3 : 2 (total yield 67 %).




**Reagents and conditions** $Br(CH_2)_3Br$, 90°C, KOH, DCE, toluene

Reaction of **1** with 1-bromo-3-chloropropane gives compound **2** in 40 % yield. (It is important to note that ketone **2** is formed as a mixture of *cis*- and *trans*-isomers if 2-ethoxycarbonylcyclododecanone is used as the starting material.[1])

One can assume that **3** is formed either by dehydrobromination of 1,3-dibromopropane and subsequent alkylation of **1** with the allyl bromide thus formed, or by dehydrobromination of the intermediate 2-(3-bromopropyl)cyclododecanone (**4**). In order to establish which mechanism occurs, bromoketone **4** was synthesized from allylketone **3** by the addition of HBr in the presence of benzoyl peroxide. Treatment of **4** with KOH under conditions of phase-transfer catalysis gave *trans*-ketone **2** as the sole product.




*i*: HBr, $Bz_2O_2$, hexane
*ii*: KOH, DCE

This result suggests that the formation of allylketone **3** in the alkylation of ketone **1** with either 1,3-dibromopropane or 1-bromo-3-chloropropane is caused by dehydrohalogenation of these dihalopropanes under

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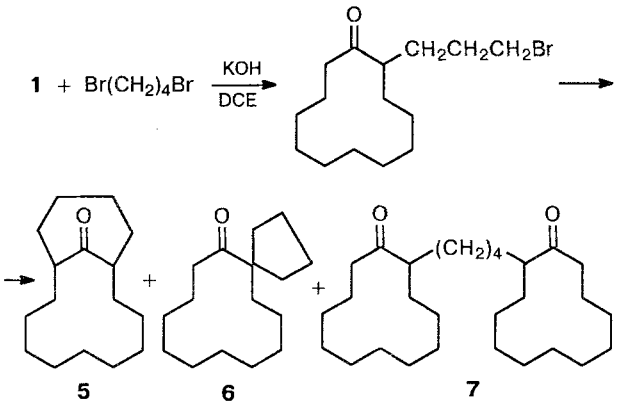
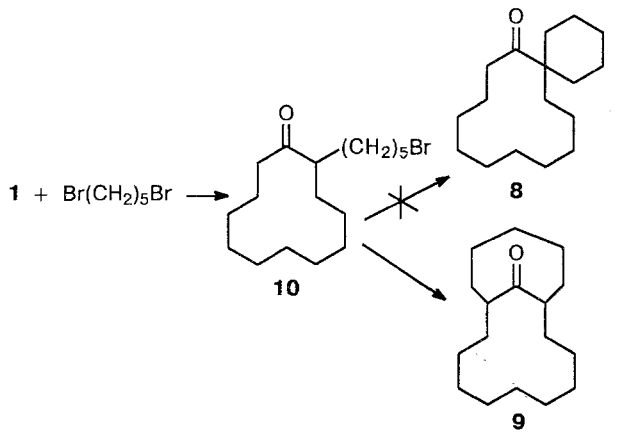
the conditions of phase-transfer catalysis. The most convenient route for preparation of ketone **2** is outlined in the above scheme; its makes use of the easily accessible allylketone **3**.[5] Unlike ketone **4**, under the action of strong bases its structural analog, 2-(3-bromopropyl)-cyclohexanone, transforms mainly to 2-oxa-bicyclo[4.4.0]decene-1(6) and gives only traces of the spirocyclic ketone.[6]

The reaction of ketone **1** with 1,4-dibromobutane gives bicyclic ketone **5** and spiroketone **6** in the ratio of 5 : 4; 1,4-bis(2-oxocyclododecyl)butane (**7**) is also isolated in a small amount.




Alkylation of ketone **1** with 1,5-dibromopentane under analogous conditions gives, contrary to our expectations, not 7-oxospiro[5.11]heptadecane (**8**), but bicyclo-[9.5.1]heptadecan-17-one (**9**), the structure of which was established by $^{13}C$ NMR.

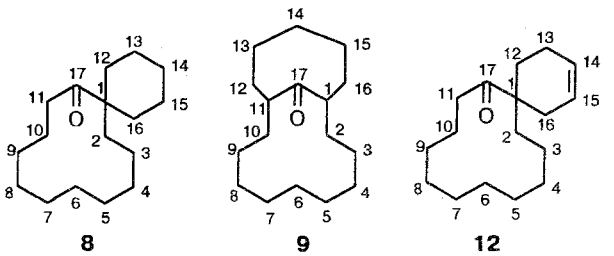



The isolated intermediate of this reaction, 2-(5-bromopentyl)cyclododecanone (**10**), also cyclizes to form exclusively bicyclic ketone **9**.

To confirm the structure of compound **9** we synthesized spiroketone **8** using the Diels—Alder reaction according to the scheme 1.

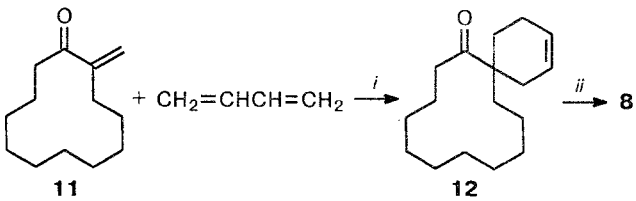
When heated with butadiene 2-methylenecyclododecanone (**11**) affords 7-oxospiro[5.11]heptadecene-2 (**12**), whose subsequent hydrogenation on Raney Ni gives spiroketone **8**. The structures of compounds **12** and **8** are confirmed by IR, $^1H$ and $^{13}C$ NMR spectra. The comparison of ketones **8** and **9** (m.p., high-performance capillary GLC, $^1H$ and $^{13}C$ spectroscopy) indicates that these compounds differ in their properties.

**Table 1.** $^{13}C$ NMR data for compounds **8**, **9**, and **12** ($CCl_4$, δ, ppm)




| Compound | 8 | 9 | 12 |
|---|---|---|---|
| C(1) | 51.81 | 52.40 | 49.93 |
| C(2) | 32.21 | 33.73 | 32.34 |
| C(3) | 23.29 | 26.85 | 21.89 |
| C(4) | 22.97 | 25.28 | 22.11 |
| C(5) | 21.67 | 26.85 | 22.62 |
| C(6) | 19.22 | 22.24 | 19.55 |
| C(7) | 21.28 | 26.85 | 22.62 |
| C(8) | 22.44 | 25.28 | 22.11 |
| C(9) | 22.03 | 26.85 | 21.37 |
| C(10) | 26.05 | 33.73 | 26.64 |
| C(11) | 37.36 | 52.40 | 35.38 |
| C(12) | 33.32 | 36.48 | 31.50 |
| C(13) | 26.49 | 27.26 | 28.26 |
| C(14) | 26.30 | 27.26 | 124.73 or 126.38 |
| C(15) | 26.49 | 27.26 | 126.38 or 124.73 |
| C(16) | 33.32 | 36.48 | 26.37 |
| C(17) | 211.04 | 219.47 | 210.25 |

**Scheme 1**




*i*: 160 °C.
*ii*: $H_2$, 20 °C, Ni/Re.

The chemical shifts of the signals in the $^{13}C$ NMR spectra of compounds **8**, **9**, and **12** are presented in Table 1.

A comparison of the $^{13}C$ NMR spectra of ketones **8** and **12** with that of **9** shows that the number of signals in the spectrum of the latter is significantly lower due to its symmetrical structure.

## Experimental

The GLC experiments were carried out with a 25 m glass capillary column with OV-17, 220 °C, He (1.5 bar).

The $^{13}C$ and $^{1}H$ NMR spectra were recorded with a Bruker-WP-200 instrument (200 MHz). 2-Allylcyclododecanone was obtained as reported in Ref. 5, and 2-methylenecyclododecanone was prepared as described in Ref. 7.

**Bicyclo[9.3.1]pentadecan-15-one (2). a.** A mixture of ketone **1** (11 g, 0.06 mol), 1,3-dibromopropane (10 g, 0.064 mol), KOH powder (9 g, 0.016 mol), and DCE (0.2 g) in toluene (45 mL) was heated at 90—100 °C with stirring for 20 h, cooled, poured into water, and the organic layer was separated, washed 2 times with water, and dried over $Na_2SO_4$. The solvent was removed, and distillation of the residue gave a fraction (9 g) with b.p. 112—120 °C (0.5 Torr), consisting of bicyclic compound **2** (60 %) and allylketone **3** (40 %) (GLC). This mixture was dissolved in pentane, frozen at −70 °C, and the precipitated crystals of ketone **2** were filtered off, m.p. 55—57 °C (*trans*-isomer) (*cf.* Ref. 1). From the mother liquor allylketone **3** was isolated by distillation, b.p. 112—114 °C (1 Torr). Application of this procedure to the reaction of ketone **1** with 1-chloro-3-bromopropane afforded a mixture of ketone **2** (65 %) and ketone **3** (35 %) obtained in 62 % yield.

**b.** A mixture of bromide **4** (3 g, 0.013 mol), KOH (3 g, 0.055 mol), and DCE (0.1 g) in toluene (20 mL) was stirred at 80 °C for 6 h. Treatment as described above gave *trans*-**2** (1.7 g, 77 %), b.p. 125—127 °C (1 Torr), m.p. 56—57 °C (MeOH) (*cf.* Ref. 1). Found (%): C, 80.81; H, 11.76. $C_{15}H_{26}O$. Calculated (%): C, 81.08; H, 11.71.

**2-(3-Bromopropyl)cyclododecanone (4).** HBr gas was bubbled through a solution of ketone **3** (2 g, 0.009 mol) in hexane (15 mL) and benzoyl peroxide (0.1 g) with stirring at 20 °C for 3 h. The mixture was poured into water, and the organic layer was separated, washed with a $NaHCO_3$ solution, and dried over $CaCl_2$. After removal of the solvent, bromide **4** (2.3 g, 84 %) was obtained, b.p. 168—170 °C (1 Torr), m.p. 30—31 °C (hexane). Found (%): C, 59.74; H, 9.09; Br, 26.24. $C_{15}H_{27}OBr$. Calculated (%): C, 59.40; H, 8.97; Br, 26.35.

**Bicyclo[9.4.1]hexadecan-16-one (5) and 7-oxospiro[4.11]hexadecane (6).** A mixture of ketone **1** (10 g, 0.055 mol), 1,4-dibromobutane (12 g, 0.055 mol), KOH (9 g, 0.16 mol), and DCE (0.2 g) in toluene (40 mL) was heated at 80—90 °C for 20 h. After the usual treatment, a mixture of products **5** and **6** (8 g, 62 %) was isolated, b.p. 146—150 °C (1 Torr) in the ratio of 5 : 4 (GLC). Crystallization from pentane gave 3 g of **5**, m.p. 85—86 °C (*cf.* Ref. 3). Found (%): C, 81.06; H, 11.85. $C_{16}H_{28}O$. Calculated (%): C, 81.36; H, 11.86. Evaporation of the mother liquor followed by fractional crystallization from MeOH afforded spiroketone **6** (1 g), m.p. 54—55 °C (*cf.* Ref. 3). Distillation of the residue gave 0.3 g (13 %) of 1,4-bis-ketone **7**, m.p. 114—116 °C (heptane). Found (%): C, 79.71; H, 11.92. $C_{28}H_{50}O_2$. Calculated (%): C, 80.38; H, 11.96. Mass spectrum (*m/z*): 418 $[M]^{+\cdot}$.

**Bicyclo[9.5.1]heptadecan-17-one (9).** A mixture of ketone **1** (10 g, 0.55 mol), 1,5-dibromopentane (12.6 g, 0.055 mol), KOH (13 g, 0.23 mol), and DCE (0.2 g) in toluene (30 mL) was heated at 80—90 °C for 20 h. After the usual treatment, ketone **9** (9 g, 66 %) was obtained, b.p. 158—160 °C (1 Torr), m.p. 70—71 °C (MeOH). $^{1}H$ NMR ($CDCl_3$, δ, *ppm*): 1.21 (*m*, 21 H); 1.49 (m, 3 H, H(13), H(14), H(15)); 1.65 (m, 2 H, H(2), H(10)); 2.02 (m, 2 H, H(12), H(16)); 2.52 (m, 2 H, $J$ = 6.2 Hz, H(1), H(11)). Found (%): C, 81.58; H, 12.04. $C_{17}H_{30}O$. Calculated (%): C, 81.60; H, 12.0. When the reaction was carried out at 60 °C for 10 h, bromide **10** was isolated, b.p. 180—200 °C (1 Torr), m.p. 38—43 °C (hexane). Found (%): C, 61.97; H, 9.54; Br, 23.70. $C_{17}H_{31}BrO$. Calculated (%): C, 61.63; H, 9.36; Br, 24.17.

**7-Oxospiro[5.11]heptadec-2-ene (12).** A solution of ketone **11** (5 g, 0.026 mol) and 1,3-butadiene (6 g, 0.01 mol) in toluene (20 mL) was heated in a metal tube at 160 °C for 10 h. Distillation gave spiroketone **12** (4.2 g, 66 %), b.p. 143—145 °C (1 Torr), m.p. 59—60 °C (MeOH). $^{1}H$ NMR ($CDCl_3$, δ, ppm): 1.24 (H(2)—H(11)); 1.65 (m, 5 H); 1.94 (m, 4 H); 2.55 (t, 3 H); 5.58 (s, 2 H, H(13)—H(14)). Found (%): C, 82.31; H, 11.34. $C_{17}H_{28}O$. Calculated (%): C, 82.25; H, 11.29.

**7-Oxospiro[5.11]heptadecane (8).** Spiroketone **12** (2 g, 0.009 mol) was hydrogenated in an autoclave over Raney Ni in 25 mL of MeOH (60 atm $H_2$, 25 °C, 10 h). The catalyst was filtered off, methanol was removed, and ketone **8** (2 g) was obtained, b.p. 145—147 °C (1 Torr), m.p. 62—63 °C (MeOH). IR (ν/cm$^{-1}$): 1700 (C=O). $^{1}H$ NMR ($CDCl_3$, δ, ppm): 1.19 (m); 1.62 (m, 5 H); 1.95 (m, 2 H); 2.01 (m, 2 H, H(2), H(10)); 2.43 (t, 2 H, H(1), H(11), $J$ = 5.7 Hz). Found (%): C, 81.64; H, 12.23. $C_{17}H_{30}O$. Calculated (%): C, 81.60; H, 12.00.

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